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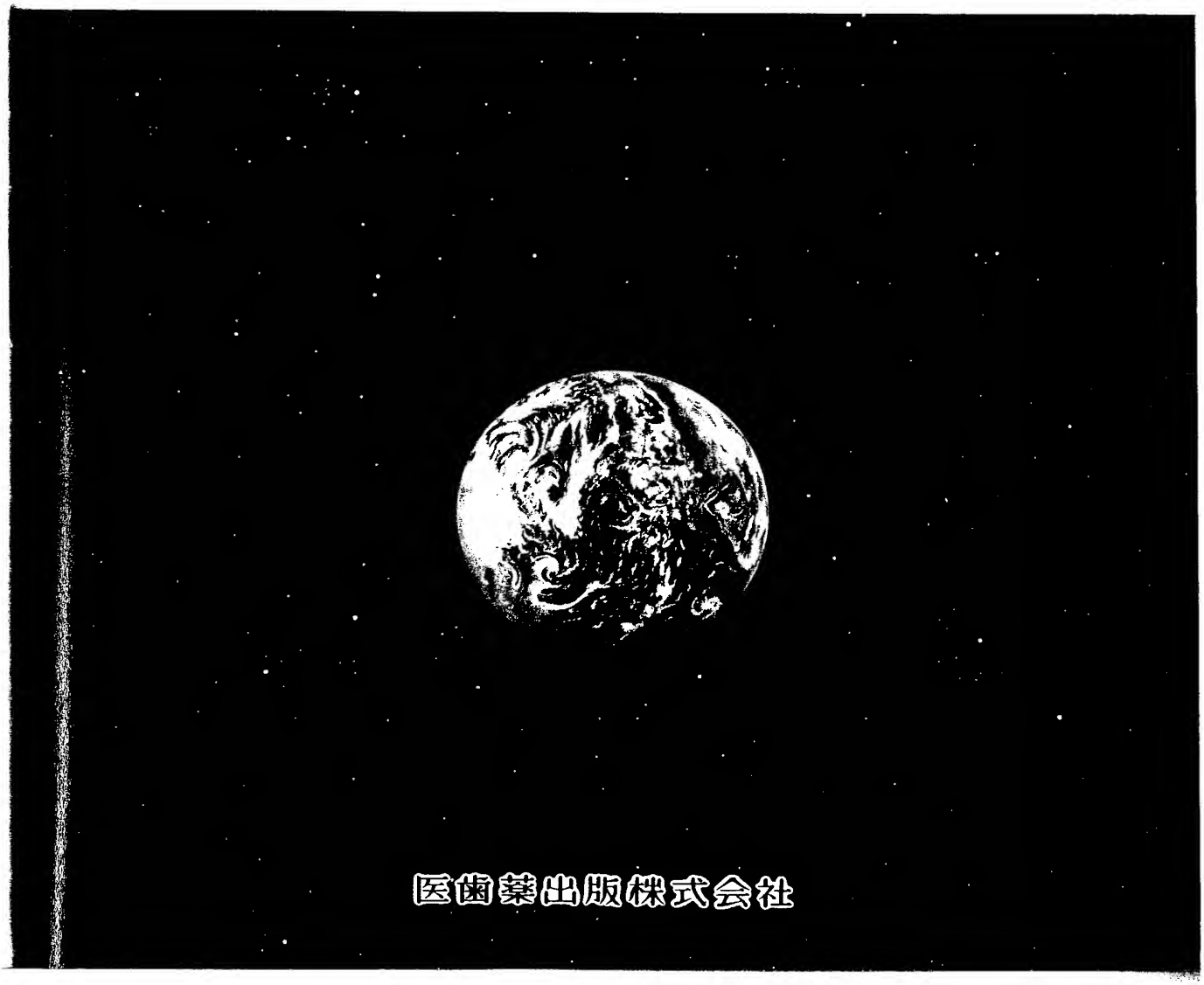
第5土曜特集

炎症性腸疾患の最新動向



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Crohn病の診断と治療の現状

馬場忠雄　佐々木雅也

◉Crohn病は1995年，診断基準（案）の改訂がなされた．また，治療に関しては成分栄養療法の有用性が確立されたほか，抗サイトカイン療法などの新しい治療法も臨床応用も試みられている．

キーワード：縦走潰瘍，敷石像，非乾絡性肉芽腫，成分栄養療法，中心静脈栄養

Crohn病は未だ病因不明の難治性疾患であるが，近年患者数が著しく増加し，平成6年度の医療費受給者証公布件数は11,337件に達している．1995年，厚生省の特定疾患，難治性腸管障害調査研究班（武藤班）においてCrohn病の診断基準が約20年ぶりに改訂された．一方，治療に関しては成分栄養療法（elemental diet）や中心静脈栄養（total parenteral nutrition）による栄養療法の有用性が確立された．また，薬物療法においても新しい薬剤の臨床成績が報告されている．

そこで，Crohn病の新しい診断基準の改訂点を中心に解説し，また栄養療法と薬物療法の基本的な治療方針のほか，近年注目されている新しい治療法についても触れたい．

■定義ならびに臨床症状

WHOのCouncil for International Organizations of Medical Sciences（CIOMS）の定義によれば，本症は“主として若い成人にみられ，線維化や潰瘍を伴う肉芽腫性病変からなり，消化管のどの部位にも起こりうる”とされ，臨床症状は病変の部位や範囲により発熱，栄養障害，貧血，関節炎，虹彩炎，肝障害などの全身合併症が起こりうると記載されている．

Diagnosis and current therapy for Crohn's disease
Tadao BAMBA and Masaya SASAKI：滋賀医科大学第二内科

臨床症状は病変の罹患範囲により異なるが，腹痛がもっとも多く，全身倦怠感，下痢などが高頻度にみられる．しかし，腹部以外の発熱，体重減少といった症状で発症する症例もみられ，診断までに時間を要することも稀ではない．また，痔瘻，難治性潰瘍，肛門周囲膿瘍，skin tagなどの肛門病変もCrohn病に特徴的な所見であり，とくに大腸病変を有するCrohn病で高率にみられる．

Crohn病の腸病変は，縦走潰瘍，敷石像，狭窄，瘻孔などが，非連続性または区域性にみられるのが特徴である．したがって，本症は，縦走潰瘍や敷石像，狭窄などの主病変の存在する部位により小腸型，小腸大腸型，大腸型に分類される．また，非定型的な特殊型として，これらの所見を欠き，アフタのみからなる病型や，盲腸虫垂限局型などもみられる．また，上部消化管のCrohn病変として口腔，食道，胃病変があるが，内視鏡診断の進歩により，これら上部消化管に病変を有する確率は，従来考えられていた以上に高率であることが確認されている．

病理学的所見では，おもにリンパ球を主体とする全層性の炎症所見がみられるほか，非乾酪性類上皮細胞肉芽腫がもっとも特徴的な所見である．

■診断基準

Crohn病の診断基準が厚生省特定疾患難治性腸管障害調査研究班（武藤班）において改訂された（表1）．本症の新しい診断基準では主要所見として縦走潰瘍，敷石像，非乾酪性肉芽腫の3つが，また副所見として縦列する不整形潰瘍，アフタ，または上部消化管と下部消化管の両者に認められる不整形潰瘍とアフタがあげられている．従来の基準（日本消化器病学会クローン病検討委員会，1976年）において主要項目とされていた非連続性または区域性病変や全層性炎症性病変は今回の基準では主要項目から削除された．また，Crohn病

表1　Crohn 病診断基準（改訂案）

Ⅰ．概念

本疾患は原因不明で，主として若い成人にみられ，浮腫，線維（筋）症や潰瘍を伴う肉芽腫性炎性病変からなり，消化管のどの部位にも起りうる．消化管以外（とくに皮膚）にも転移性病変が起こることがある．原著では回腸末端を侵す(回腸末端炎)と記載されたが，その後，口腔から肛門までの消化管のあらゆる部位に起こりうることがわかった．臨床像は病変の部位や範囲による．発熱，栄養障害，貧血，関節炎，虹彩炎，肝障害などの全身性合併症が起こりうる

〔WHO の CIOMS（Council for International Organizations of Medical Sciences. 医科学国際組織委員会）による概念（1973）を一部改訂〕

Ⅱ．主要事項

1．好発年齢：10 歳代後半から 20 歳代

2．病変部位：大多数は小腸や大腸，またはその両者に縦走潰瘍な敷石像などの病変を有する

3．臨床症状：腹痛，下痢，体重減少，発熱，肛門病変などがよくみられる症状である
ときに虫垂炎に類似の症状，腸閉塞，腸穿孔，大出血で発症する．また，腹部症状を欠き，肛門病変や発熱（不明熱）で発症することもある

4．臨床所見：

A．消化管病変

1）腸病変
- a．縦走潰瘍[注1)]
- b．敷石像[注2)]
- c．腸管の狭小，狭窄
- d．非連続性または区域性病変（いわゆる skip lesion）
- e．内瘻（腸-腸瘻，腸-膀胱瘻，直腸-膣瘻など）
- f．外瘻（腸-皮膚瘻）
- g．不整形潰瘍
- h．多発アフタ[注3)]

2）肛門病変
- a．難治性痔瘻
- b．肛門周囲膿瘍
- c．裂肛
- d．潰瘍
- e．肛門皮垂（skin tag）など

3）胃・十二指腸病変
- a．多発アフタ
- b．潰瘍
- c．狭窄
- d．敷石像など

B．消化管外病変

1）血液　：貧血，低蛋白血症など
2）関節　：腸性関節炎，強直性脊椎炎など
3）皮膚　：口内アフタ，結節性紅斑，壊死性膿皮症，多形滲出性紅斑など
4）眼　　：虹彩炎，ブドウ膜炎など
5）栄養代謝：成長障害，微量元素欠乏，ビタミン欠乏(ビタミン-B_{12}，葉酸など)，アミロイドーシスなど
6）悪性腫瘍：腸癌など
7）その他　：原発性硬化性胆管炎

5．病理学的所見

A．切除標本肉眼所見

1）縦走潰瘍[注1)]
2）敷石像[注2)]

B．切除標本組織所見

1）非乾酪性類上皮細胞肉芽腫（局所リンパ節にみられることがある）[注4)]
2）全層性炎症[注5)]
3）裂溝
4）潰瘍

C．生検組織所見

非乾酪性類上皮細胞肉芽腫[注4)]

[注1)] 腸管の長軸方向に 4〜5 cm 以上の長さを有する潰瘍で活動期潰瘍では，近傍に炎症性ポリープや敷石像を伴うことが多い．虚血性大腸炎で縦走潰瘍を認めることがあるが，炎症性ポリポーシスや敷石像を伴うことはまれである．潰瘍性大腸炎で縦走潰瘍を認めることがあるが，その周辺粘膜は潰瘍性大腸炎に特徴的な所見を呈する

表3　つづき

[注2] 縦走潰瘍とその周辺小潰瘍間の大小不同の密集した粘膜隆起であり，密在した炎症性ポリポーシスもこれに含める．虚血性大腸炎の場合，肉眼標本上で浮腫や残存粘膜島が敷石像類似の所見を呈することがあるが，その高さは低く，発赤調が強い
[注3] 本症では縦列することがある
[注4] 非乾酪性類上皮細胞肉芽腫は，腸結核でも認められることがある
[注5] おもにリンパ球からなる集簇巣が消化管壁全層にみられるもの

III．診断の基準

1．主要所見
A．縦走潰瘍
B．敷石像
C．非乾酪性類上皮細胞肉芽腫
2．副所見
a．縦列する不整形潰瘍またはアフタ
b．上部消化管と下部消化管の両者に認められる不整形潰瘍またはアフタ

確診例：1．主要所見のAまたはBを有するもの[注6,7]
2．主要所見のCと副所見のいずれか1つを有するもの

疑診例：1．副所見のいずれかを有するもの[注8]
2．主要所見のCのみを有するもの[注9]
3．主要所見AまたはBを有するが虚血性大腸炎，潰瘍性大腸炎と鑑別が出来ないもの

[注6] A．縦走潰瘍のみの場合，虚血性大腸炎や潰瘍性大腸炎を除外することが必要である
[注7] B．敷石像のみの場合，虚血性大腸炎を除外することが必要である
[注8] 副所見bのみで疑診とした場合は同所見が3カ月恒存することが必要である
[注9] 腸結核などの肉芽腫を有する炎症性疾患を除外することが必要である

IV．病型分類

本症の病型は縦走潰瘍，敷石像または狭窄の存在部位による（例：小腸型，小腸大腸型，大腸型，直腸型，胃・十二指腸型など），これらの所見を欠く場合は特殊型とする．特殊型には多発アフタ型や盲腸虫垂限局型などがある

の初期像として注目されている縦列するアフタ病変などが副所見としてあげられている．

病理学的所見としては非乾酪性肉芽腫の検出が重要である．とくに，縦走潰瘍やcobblestone appearanceなどの活動期主病変から連続切片を作成し，検討した結果では，約80%と高率に肉芽腫が検出されることが確認されている[1]．しかし，症例により，あるいは病期や生検部位により肉芽腫の検出率は異なる．したがって，本症は，造影X線検査，内視鏡検査，および内視鏡下生検組織による病理学的診断法などを適切に組み合わせ，総合的に診断する．

鑑別すべき疾患には，潰瘍性大腸炎のほか，感染性腸炎，とくにアメーバ赤痢や腸結核，*Campylobacter*腸炎，*Yersinia*腸炎，さらに，抗生物質起因性腸炎，腸型Behçet病，単純性潰瘍などがある[2]．炎症性腸疾患の鑑別診断において，病変の広がり分布などをとらえるには造影X線検査が優れているが，炎症の程度や病変の形態，性状などをみるには内視鏡検査がよい．また，感染性腸炎や抗生物質起因性腸炎では食事や服薬薬剤に関する詳細な問診や，糞便中の細菌検査や塗抹鏡検などが重要である．とくに重症，あるいは縦走潰瘍を形成する潰瘍性大腸炎との鑑別は困難なことも多く，生検組織や手術標本からも確定診断できず，indeterminate colitisとされる症例もみられる．

Crohn病では免疫異常，とくに単球/マクロファージ系細胞の機能異常が示唆されているが，これらを診断に応用するには至っていないのが現状である．また，遺伝的素因としてHLA-DR 4やDRw-53，DQw-3との関連が報告されている．

■ Crohn病の治療の現状

Crohn病の治療の考え方としては，炎症を抑え，栄養状態の改善をはかる内科治療が主とされている．狭窄や瘻孔形成などにより手術を施行する場合にも，腸管の切除範囲はなるべく小範囲にとどめる狭窄形成術（stricture plasty）などを行うのが原則である．

内科治療は栄養療法と薬物療法に分けられる．以下に，厚生省特定疾患消化吸収障害調査研究班，難治性腸管障害調査研究班による治療指針[3]を中

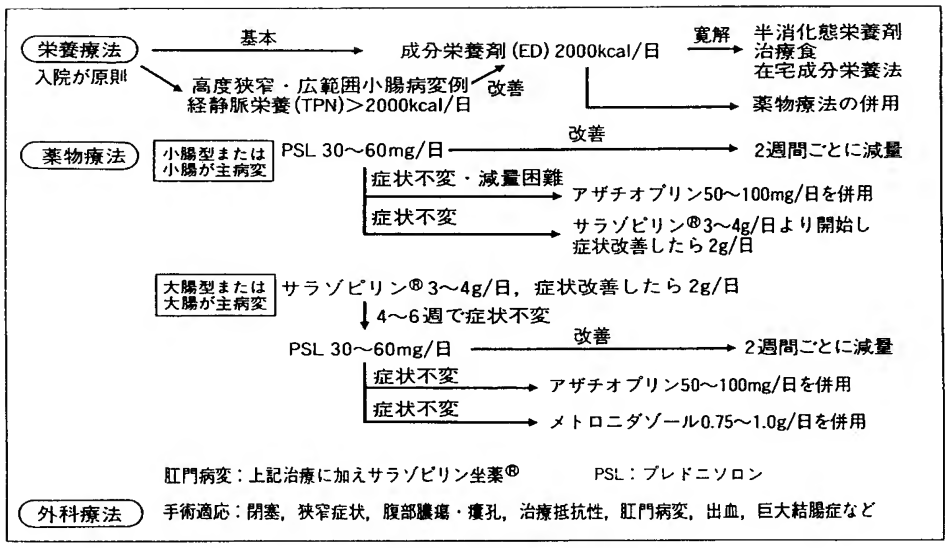

図1　Crohn病の治療指針（案）[3]

心に，それぞれの基本的な考え方を述べる．

1．栄養療法

成分栄養剤（elemental diet）や中心静脈栄養（total parenteral nutrition）による栄養療法はCrohn病のprimary therapyとされ[4]，その有用性は広く認められている．栄養療法は，腸管安静や栄養状態の改善のほか，腸管内の食事抗原の除去がCrohn病の免疫異常を是正するのに大きい意味をもつと考えられている．したがって，Crohn病においては栄養療法によって栄養状態の改善が得られるばかりでなく，腸管病変の治癒や炎症反応の改善も期待できる．また，瘻孔についても栄養療法によって閉鎖する症例も多い．

Crohn病の栄養療法の治療指針に基づき，活動期と非活動期Crohn病の栄養療法について述べる．

活動期Crohn病でも病勢が重篤な場合，すなわち高度の狭窄や瘻孔形成がみられる場合，下痢が頻回な場合，栄養状態が著しく低下している場合には中心静脈栄養により腸管の安静をはかる．病状が改善すれば，引き続き経腸栄養療法に切り替える．一方，病勢が重篤でない場合には最初から経腸栄養療法を行う．

経腸栄養療法では成分栄養剤を経鼻チューブを用いて低濃度，低用量から開始し，しだいに2,000 kcal/day以上の維持量へと漸増する．緩解が得られれば，維持療法へと移行する．中心静脈栄養療法や成分栄養療法中には脂肪乳剤の経静脈投与が必要である．

長期にわたり成分栄養療法を行う場合には微量元素の欠乏や腸粘膜萎縮などに注意する必要がある．とくに，現在用いられている成分栄養剤には亜鉛やセレンなどが必要量添加されておらず，適宜これらを補充し，欠乏症の予防に努めることが必要である[5]．

また，成分栄養剤のみならず，半消化態栄養剤でも有効な治療成績が得られ，ほぼ同等との評価もあり[6]，治療に用いるには病型や消化吸収機能も考慮して製剤を選択し，また各種の栄養パラメータを用いた栄養評価により治療効果を判定する．

緩解期においても成分栄養剤などによる在宅経腸栄養療法の有効性が確認されている．とくに1日30 kcal/B.W.以上の成分栄養剤による栄養療法ではきわめて高い緩解維持効果を認めることが報告されている（図2）[7]．また，製剤の選択には患者のQOLやADLも考慮し，経口的に摂取可能な半消化態栄養剤やペプチド経腸栄養剤などを用いてもよい．食事は，低脂肪，低残渣食を併用し，スライド方式で徐々に食事を増量する．Crohn病

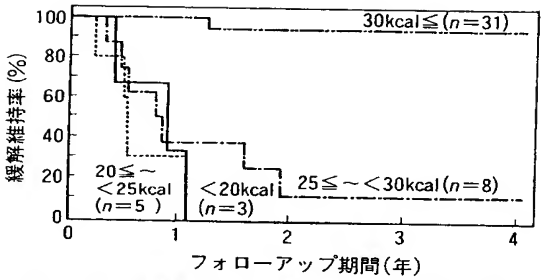

図2　成分栄養剤による緩解維持率（兵庫医大第四内科，福田能啓ら[7]）

の栄養療法では普通食へと移行する過程で再燃する症例も多いので，再燃徴候がみられたら食事を中止し，完全成分栄養療法に変更する．

2．薬物療法

Crohn病の薬物療法としては，サラゾピリン®，メサラジン®，副腎皮質ステロイド，免疫抑制剤，メトロニダゾールなどが用いられるが，病変の罹患部位により有効性が異なる．サラゾピリン®は大腸内の腸内細菌により分解されて生じる5-アミノサリチル酸（5-ASA）が有効成分であり，とくに大腸型のCrohn病に有用である．

本年6月より5-アミノサリチル酸を徐放性腸溶剤であるエチルセルロースによりコーティングしたペンタサ®（メサラジン）が使用可能となり，大腸型Crohn病はもちろんのこと小腸型Crohn病にも有効性が期待される．

小腸型，あるいは小腸病変が主体の症例はプレドニゾロン30～60 mg/dayの投与を行い，改善がみられれば2週間ごとに減量する．症状が不変あるいは減量困難な場合にはアザチオプリン（50～100mg/day）やペンタサ® 1,500～3,000 mg/dayの併用を行う．大腸型，あるいは大腸病変が主体の症例はサラゾピリン® 3～4g/day，ペンタサ® 1,500～3,000 mg/dayで治療を開始し，症状が不変であればプレドニゾロン30～60 mg/dayを併用する．これでも改善がみられなければアザチオプリン（50～100 mg/day）またはメトロニダゾール（750～1,000 mg/day）を併用する．

なお，6-mercaptopurine少量投与が瘻孔の治療や緩解維持に有効との報告もある[8]．

肛門病変に対してはサラゾピリン® 坐薬も有効であり，メトロニダゾール（750～1,000 mg/day）も用いられる．

また，炎症性腸疾患の病態にアラキドン酸代謝産物であるロイコトリエンB_4（LTB_4）やトロンボキサンA_2（TXA_2）などが深く関与していることが知られている．これらの合成阻害薬や拮抗薬は潰瘍性大腸炎において有用性が報告されているが，Crohn病においても臨床治験が行われる予定である．

一方，抗サイトカイン療法では抗TNF抗体やIL-10などによるCrohn病の治療が欧米では臨床的に検討されている．とくに抗TNF抗体による優れた治療成績がVan Dullemenらにより報告され[9]，従来の薬物治療とまったく異なった治療法として注目されている．

また，ステロイド剤においても肝での代謝が速く，副作用の少ない製剤の臨床治験も行われている．

3．その他

近年，炎症性腸疾患の新しい治療法として白血球除去療法が試みられている．白血球の除去方法や除去フィルターの種類によっても治療成績は異なるが，潰瘍性大腸炎における高い有効率に比べ，Crohn病においてはその評価は確立されていない[10]．

■おわりに

Crohn病は年々患者数が増加し，診断技術の向上により初期病変と考えられる症例もみられるようになった．しかし，いまだ病因は明らかにされておらず，根本的な治療法も確立されていない．成分栄養剤をはじめとする栄養療法は緩解維持にも有効で，QOLの点からも優れた治療法であるが，コンプライアンスの低下により再燃がみられる．近年，サイトカインを中心とした免疫学的な病態の研究により抗サイトカイン療法も臨床応用が開始されており，治療に関しても新しい今後の展開が期待される．

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Diagnosis and Current Therapy for Crohn's Disease

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Abstract

Diagnostic criteria (draft) of Crohn's disease were revised in 1995 and a usefulness of elemental diet therapy was established for its therapy. Furthermore, new therapies such as anti-cytokine therapy have been tried in their clinical application.

*

Key words: Longitudinal ulcer, Cobble stone appearance, Non-caseous granuloma, Elemental diet therapy, Total parenteral nutrition

Introduction

Crohn's disease is an intractable disease and its cause is still unclear. Patients suffering from the disease have been markedly increasing in recent years and reached to 11,337 cases in the number of certificates receiving medical cost coverage in 1994. In 1995, The Specific Diseases and Intractable Bowel Disturbance Study Group (Muto group) in The Ministry of Health and Welfare revised the diagnostic criteria of Crohn's disease for the first time in 20 years. While usefulness of nutritional therapies such as elemental diet and total parenteral nutrition was established. Furthermore, clinical results of new drugs have been reported in medical therapy.

Here, revised points of new diagnostic criteria are mainly explained and new therapies focused attention in recent years and fundamental therapeutic approaches of nutritional therapy and drug therapy will be discussed.

■ Definitions and clinical symptoms

According to the definition of Council for International Organization of Medical Sciences

(CIOMS) in WHO, the disease is "mainly found in young adults and composed of granulomatous lesion accompanying fibrosis and ulcers and may develops in any place in the digestive tract". The clinical symptoms are reported that may cause systemic complications such as fever, nutritional disturbance, anemia, arthritis, iritis and hepatopathy by the site and area of the lesion.

The clinical symptoms differ by the area of diseased lesion and abdominal pain is most frequently found and general malaise and diarrhea are frequently observed. However, some cases show symptoms such as fever and body weight loss other than abdominal symptoms and not a few cases require times to find definite diagnosis. In addition, anal lesions such as anal fistula, intractable ulcer, perianal abscess and skin tag are typical findings in Crohn's disease and are particularly and frequently found in Crohn's disease accompanied with colon lesions.

Intestinal lesions of Crohn's disease are typically longitudinal ulcer, cobble stone appearance, stricture and fistula, and are discontinuously or segmentally found. Therefore, the disease is classified small intestinal, small and large intestinal, and large intestinal types by the site of main lesion such as longitudinal ulcer, cobble stone appearance and stricture. Furthermore, disease type solely composed of aphtha without these findings as an atypical specific type, or cecum and appendix restricted type can be found. Crohn's lesions in upper digestive tract include oral, esophageal and gastric lesions and their development at higher ratios in the upper digestive tract than those previously presumed is confirmed by the development of endoscopic diagnosis.

Pathological findings include transmural inflammation mainly composed of lymphocytes and most typically show non-caseous epithelioid cell granuloma.

■ Diagnostic criteria

The diagnostic criteria of Crohn's disease were revised by The Specific Diseases and Intractable Bowel Disturbance Study Group (Muto group) in The Ministry of Health and Welfare (Table 1).

■ Table 1 Diagnostic criteria of Crohn's disease (draft for revision)

I. Conception

The cause of the disease is unclear and mainly observed in young adults and composed of granulomatous inflammatory lesion accompanying with edema, fibrous(muscular) disease or ulcer, and may develop in any place in the digestive tract. The disease may occur at other than the digestive tract (particularly skin) as a metastatic lesion. In the original article, it was recorded to infiltrate in the terminal ileum (inflammation of terminal ileum), however, its development in all places of digestive tract from oral cavity to anus was found. The clinical images depend on the site and area of the lesion. Systemic complications such as fever, nutritional disturbance, anemia, arthritis, iritis and hepatopathy may occur.

[Partial revision of the conception (1973) of CIOMS (Council for International Organization of Medical Sciences) in WHO]

II. Main features

1. Frequent ages: Late teens to 20s years.
2. Site of lesion: Mostly in small and/or large intestines with lesions such as a longitudinal ulcer or a cobble stone appearance.
3. Clinical symptoms: Abdominal pain, diarrhea, body weight loss, fever and anal lesion are frequently observed.

   Sometimes it develops with appendicitis-like symptoms, ileus, perforation of intestine and massive bleeding. The development without abdominal symptom accompanying with anal lesion and fever (unknown cause) may occur.

4. Clinical findings:

A. Digestive tract lesions

1) Intestinal lesions
   a. Longitudinal ulcer[1)]
   b. Cobble stone appearance[2)]

		c. Narrowing, stricture of intestine
		d. Discontinuous or segmental lesion (so-called skip lesion)
		e. Internal fistulas (intestine-intestine, intestine-bladder, rectum-vagina, etc.)
		f. External fistula (intestine-skin)
		g. Irregular ulcer
		h. Multiple aphtha[3)]
2)	Anal lesions	a. Intractable fistula
		b. Perianal ulcer
		c. Anal fissure
		d. Ulcer
		e. Anal skin tag, etc.
3)	Gastric · duodenal lesions	a. Multiple aphtha
		b. Ulcer
		c. Stricture
		d. Cobble stone appearance, etc.

B. Lesions other than digestive tract

1) Blood : Anemia, hypoproteinemia, etc.

2) Joints : Intestinal arthritis, ankylosing spondylitis, etc.

3) Skin : Oral aphtha, erythema nodosum, necrotic pyoderma, multiple exudative erythema, etc.

4) Eyes : Iritis, uveitis, etc.

5) Nutritional metabolisms: Disturbance of growth, minor element deficiency, vitamin deficiency (vitamin B_{12}, folic acid, etc.)

and amyloidosis, etc.

6) Malignant tumors : Intestinal cancer, etc.

7) Others : Primary sclerosing cholangitis

5. Physiological findings

A. Gross observations of resected specimen

1) Longitudinal ulcer[1)]

2) Cobble stone appearance [2)]

B. Tissue observation of resected specimen

1) Non-caseous epithelioid cell granuloma (may be found in local lymph node)[4)]

2) Transmural inflammation[5)]

3) Fissure

4) Ulcer

C. Tissue observations of biopsied specimen

Non-caseous epithelioid cell granuloma[4)]

[1)] An ulcer extending 4-5 cm or longer in longitudinal direction of intestine often accompanies nearby inflammatory polyp and cobble stone appearance in active stage ulcer. Ischemic colitis may show longitudinal ulcer, however, rarely accompanies inflammatory polyp or cobble stone appearance. Ulcerative colitis may show longitudinal ulcer, however, peripheral mucous membrane shows characteristic findings of ulcerative colitis.

[2)] Longitudinal ulcer accompanies dense mucous protuberances with uneven sizes of small ulcers surrounding it including dense inflammatory polyposis. Edema and residual mucous membrane islets may show low intense reddening cobble stone-like appearance in the ischemic colitis.

[3)] The symptom may be in lines.

[4)] Non-caseous epithelioid cell granuloma may also be found in intestinal

tuberculosis.

[5] The symptom mainly composed of aggregated foci of lymphocytes are found in transmural digestive tract.

III. Diagnostic criteria

1. Main findings

A. Longitudinal ulcer

B. Cobble stone appearance

C. Non-caseous epithelioid cell granuloma

2. Associated findings

a. Irregular ulcers in columns or aphthae

b. Irregular ulcers or aphthae observed in upper and lower digestive tracts

Cases with definite diagnosis: 1. Cases having A or B in the main finding[6,7] .

2. Cases having C in the main findings and one of the associated finding.

Cases with suspected diagnosis: 1. Cases having one associated finding[8].

2. Cases solely having C in the main finding[9].

3. Cases having A or B in the main finding but could not be differentiated from ischemic colitis or ulcerative colitis.

[6] A. In case of solely with longitudinal ulcer, ischemic colitis and ulcerative colitis must be excluded.

[7] B. In case of solely with cobble stone appearance, ischemic colitis must be excluded.

[8] Cases of suspected diagnosis solely by associated finding b, the finding must be observed for three months.

[9] Inflammatory diseases having granulomas such as intestinal tuberculosis

must be excluded.

IV. Classification of disease type

The disease type of the present disease depends on the site of longitudinal ulcer, cobble stone appearance or stricture (e.g. small intestine type, small-large intestine type, large intestine type, rectal type and gastric・duodenal type), a disease without these findings is referred as a specific type. The specific type includes such as multiple aphtha type and cecum appendix localized type.

The new diagnostic criteria of the present disease have three main findings of longitudinal ulcer, cobble stone appearance and non-caseous granuloma, and accessory findings of irregular ulcer in columns, aphthae, or irregular ulcers and aphthae observed in both upper and lower digestive tracts may be enumerated. Discontinuous or segmental lesions and transmural inflammatory lesion deemed as main items in the conventional criteria (The Japanese Society of Gastroenterology, Crohn's disease study committee, 1976) were deleted from the main items in the present criteria. In addition, aphtha lesions in columns focused attention as an initial appearance of Crohn's disease is picked up as an accessory finding.

Detection of non-caseous granuloma as a pathological finding is important. Particularly, preparation of successive specimen in active stage lesion such as longitudinal ulcer and cobble stone appearance, and their investigation confirmed detection of granuloma at a high rate of about 80%[1]. However, detection rates of granuloma are different by the cases, disease stage or the site of biopsy. Therefore, diagnosis of the disease shall be comprehensively carried out by suitable combinations of a contrast X-ray examination, an endoscopic examination and a pathological diagnosis for a biopsied tissue under endoscopic observation.

Diseases to be differentiated include such as infectious enteritis, especially amoebic dysentery, intestinal tuberculosis, *Campylobacter* enteritis and *Yersinia* enteritis, furthermore, antibiotic caused enteritis, intestinal Behçet disease and simple ulcer in addition to ulcerative colitis[2]. The contrast

X-ray examination is excellent to grasp the spreading and distribution of lesions for the differential diagnosis of inflammatory intestinal diseases, however, the endoscopic examination is preferable to grasp the degree of inflammation, and form of the lesions and features. In addition, detailed interviews for diet and administering drug, and bacteriological examination of stool and microscopic smear examinations, etc. are important. Particularly, differentiation from severe or longitudinal ulcer forming ulcerative colitis is often difficult and no definite diagnosis may be done from biopsied or surgically resected specimen in some cases, and cases deemed as indeterminate colitis are experienced.

Immune abnormality, particularly abnormal functions of monocytes/macrophage cells are suggested in Crohn's disease, however, no application for the diagnosis is established at present. Furthermore, relationships with HLA-DR4 , DRw-53 and DQw-3 as genetic factors are reported.

■ Present status of Crohn's disease treatment.

An idea for the treatment of Crohn's disease is mainly composed of medical treatment such as suppression of inflammation and improvement of nutritional conditions. Surgical treatment for the management such as stricture and fistulation is principally carried out as far as possible to narrow the area of resection of intestine such as stricture plasty.

Medical treatments are divided into nutritional therapy and drug therapy. Their fundamental idea will be described mainly according to the therapeutic guideline of The Specific Diseases Digestive Tract Absorption Disturbance Study Group and The Intractable Bowel Disturbance Study Group in The Ministry of Health and Welfare[3].

1. Nutritional therapy

Nutritional therapy with elemental diet or total parenteral nutrition is deemed as a primary therapy of Crohn's disease[4], and its usefulness is widely recognized. The nutritional therapy is considered having marked significance in the correction of immune abnormality of Crohn's disease by the removal of meal derived antigen in the intestine in addition to intestinal rest and improvement of nutritional conditions. Therefore, the nutritional therapy of Crohn's disease gives not only the improvement of nutritional conditions but also curing of intestinal lesion and

improvements of inflammatory response can be expected. In addition, many cases showed closure of fistulae by the nutritional therapy.

Nutritional therapy of Crohn's disease in active and non-active stages according to the therapeutic guideline of nutritional therapy of Crohn's disease is described.

Total parenteral nutrition is performed to make rest the intestines for the markedly declined nutritional conditions due to frequent diarrhea in case of extensive stricture or fistulation under severe disease condition of active stage Crohn's disease. After the improvement of disease conditions, an alternative enteral feeding is followed. On the other hand, the enteral feeding is performed from the start of treatment for those under nonserious disease condition.

The enteral feeding is started through a nasal tube from low concentration and low dose of the elemental diet and gradual increase to a maintenance dose at 2,000 kcal/day or over. After attainment of remission, the therapy will be changed to a maintenance therapy. An intravenous administration of fat emulsion preparation is required during the total parenteral nutrition or the elemental diet.

Care should be taken for the lack of trace elements or atrophy of intestinal mucous membrane for the long period elemental diet. Particularly, conventional elemental diet used at present contains no required amount of zinc or selenium and must be careful to suitably supply them to prevent the deficiency disease[5].

In addition, effective therapeutic results can be obtained with not only the element diet but also partially digested nutrient and a study reported nearly equivalent effect[6]. Preparations were selected in consideration of disease type, and digestion and absorption functions, and the therapeutic effect is judged according to the nutritional evaluation using various nutritional parameters.

Efficacy of the enteral nutrition with the elemental diet at home in remission stage was confirmed. Particularly, a nutritional therapy with the elemental diet at 30 kcal/B.W./day or over was reported to exhibit very high remission maintaining effect (Fig. 2)[7].

Fundamentals Remission

Nutritional therapy ——→ Elemental diet (ED) 2,000 kcal/day ——→

Hospitalization is general rule

A case with extensive stricture・wide range lesion in small intestine

Improvement

Total parenetral nutrition (TPN) > 2,000 kcal/day

Improvement

Half digested nutrient therapeutic diet

Elemental diet at home

Accompanied with drug Therapy

Improvement

Drug therapy

PSL 30-60 mg/day ——→ Decrease at every other week

Small intestine type or main lesion in small intestine

No change in symptoms・difficult in decrease ——→

No change in symptoms ——→

Co-administration of azathiopurine at 50-100 mg/day

Start of administration of Salazopyrine® at 3-4 g/day and decrease to 2 g/day with improved symptoms.

Large intestine type or main disease in large intestine

Salazopyrine® at 3-4 g/day and decrease to 2 g/day with improved symptoms.

|No change in symptoms

↓ in 4-6 weeks

PSL 30-60 mg/day ——→

Improvement

Decrease in every 2 weeks

No change in symptoms ——→

No change in symptoms ——→

Co-administration of azathiopurine at 50-100 mg/day

Co-administration of metronidazole at 0.75-1.0 g/day

Anal lesion: Salazopyrine® suppository PSL: Prednizolone

in addition to the above mentioned therapy

Surgical therapy Indication of operation: occlusion, stricture symptom, abdominal abscess, fistula, resistant to therapy, anal lesion, bleeding, megacolon and etc.

Fig. 1 Therapeutic guideline of Crohn's disease (Draft)[3)]

Remission maintenance rate (%)

Follow up period (year)

Fig. 2 Remission maintenance rate with elemental diet

(Y. Fukuda *et al.*[7)], Hyogo College of Medicine, 4th Dept. of Internal Medicine)

In addition, a partially digested orally applicable nutrient and a peptide enteral diet may be used in consideration of QOL and ADL of the patient for the selection of preparations. The meals are

accompanied with low fat and less residual meals and are gradually increased by a sliding method. Crohn's disease often flare up again in the process of transfer from nutritional therapy to common meals and meals must be discontinued with the sign of flare up and changed to complete nutritional therapy.

2. Drug therapy

Drug therapy of Crohn's disease uses such as Salazopyrin®, mesalazine, an adrenocorticosteroid, an immunosuppressant and metronidazole, and their efficacy varies with the site of lesion. Salazopyrin® is decomposed by intestinal bacteria in large intestine and provides an effective component, 5-aminosalicylic acid (5-ASA), and particularly effective against large intestine type Crohn's disease.

A slow releasing of 5-aminosalicylic acid preparation coated with intestinal slowly soluble ethylcellulose, Pentasa®, became available in last June and its efficacy is expected not only against large intestine type Crohn's disease but also against small intestine type Crohn's disease.

Patients with the small intestine type or those mainly with small intestinal lesion are administered predonisolone 30-60 mg/day and the dose is decreased every two weeks if the symptom shows improvement. Patients without changes in the symptom or those with difficulties in the reduction of doses may be alternatively treated with a co-administration of azathiopurine (50-100 mg/day) or Pentasa® (1,500-3,000 mg/day). Treatment of patients with large intestine type or mainly with large intestinal lesion will be started by the administration of Salazopyrin® 3-4 g/day or Pentasa® 1,500-3,000 mg/day and predinisolone will be co-administered if the symptom still shows no change. Furthermore, azathiopurine (50-100 mg/day) or metronidazole (750-1,000 mg/day) will be co-administered for those remaining without improvement.

In addition, administration of a small amount of 6-mercaptopurine was reported effective in the treatment and maintenance of remission of fistula[8)].

Salazopyrin® suppository is effective against anal lesion and metronidazole (750-1,000 mg) is also used.

Furthermore, a close relationship between pathological condition of inflammatory bowel disease

and arachidonic acid metabolites leukotriene B_4 (LTB_4) and thromboxane A_2 (TXA_2) is known. Usefulness of these synthetic inhibitors and antagonists in ulcerative colitis was reported and their clinical trial against Crohn's disease will be performed.

While an anti-TNF antibody and IL-10 in the treatment of Crohn's disease as an anti-cytokine therapy of Crohn's disease is under investigations in clinical trial in Europe. Particularly, an excellent therapeutic result with an anti-TNF antibody was reported by Van Dullemen *et al.*[9], and was focused attention as a quite different therapy from conventional drug therapy.

Furthermore, steroidal drug preparations with rapid metabolism in liver and few adverse reactions are under clinical trial.

3. Others

Recently, a new therapeutic method of leukocyte removal therapy was tried in inflammatory intestinal diseases. The therapeutic results differ by the removal method or type of removal filter and no evaluation is established in the treatment of Crohn's disease in comparison with the high effective rate in ulcerative colitis[10].

■ Conclusion

The number of patients with Crohn's disease has been increasing in recent years and cases considered as initial stage lesions can be detected by the progress of diagnostic technology. However, no cause of the disease is clear without establishment of ultimate solution. The nutritional therapies including elemental diet are effective in the maintenance of remission and excellent in view of QOL, however, declined compliance shows relapse. Recently, studies on immunological pathology mainly carried out in cytokine started for the clinical application of an anti-cytokine therapy and future development in the treatment is expected.